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Mini-review

Role of endogenous retroviruses in human immune disorders and simian evolution

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Various endogenous retroviruses (ERVs) have infiltrated the genomes of simians and humans as they evolved. Different types of ERVs have endogenised in the primates throughout their evolutionary journey and serve as crucial indicators in defining the phylogeny of their hosts. The ERVs also play a crucial role in various immune disorders through their active particles, such as the production of autoantigens in cases of autoimmunity-like scenarios. Instead of acting through their particles, some ERV sequences directly influence immunoregulatory genes. Furthermore, genetic variation in these ERV sequences regulates the linked genes and influences their evolutionary fitness. The *CD5* and *FABP7* genes are directly impacted by ERV sequences and are associated with leukaemia. ERV, linked to both of these genes, plays two distinct roles: it influences the immune system and determines phylogeny. By keeping these two genes in mind, this review has explored the ERVs-immunity axis, ERVs' role in Simian phylogeny, and their conclusive impact on human health.

Keywords: Endogenous retrovirus, Simians, Phylogeny, *CD5*, *FABP7,* Leukaemia

Introduction

With the evolution of simians (monkeys, apes) and humans, various endogenous retrovirus particles have integrated into their genomes, serving as informative markers for phylogenetic analyses[1,2]. The era of integration of various endogenous viruses coincided with the divergence era of major primate species, e.g. at the time of separation of New World Monkeys (NWM) from Old World Monkeys (OWM), a group E endogenous retrovirus (ERVE) integrated into the OWMs[3,4]. Various functionally dormant retroviruses are implicated in gene expression in immune cells[5]. The immune system is key to the evolutionary fitness of an organism[6]. Hence, many endogenous retroviruses (ERVs) establish a link between the phylogeny and immunity of a species. We will review the ERVs of different classes, like ERV-E, ERV-K, ERV-W and ERV-V and their immunological interference[7-10]. These ERVs are implicated in various clinical conditions, including leukaemia, psoriasis, and autoimmunity[11-13]. Also, they certainly have evolutionary roles in the journey of primate phylogeny[14] This review will overview the Human endogenous retroviruses (HERVs) entangled with the human immune system and establish an evolutionary link with the other simians.

Evolution of the different groups of endogenous retroviruses in simians and humans

ERVs represent retroviruses that embed into the host's genome, participating in their evolutionary journey[15]. These retroviruses are comprised of non-coding RNAs, mostly the long terminal repeats (LTRs), protein-coding sequences which include *gag* (matrix capsid and nucleocapsid proteins); *pol* (polymerase); and *env* (envelope protein), a primer binding site (PBS) which interacts with primer tRNA for reverse transcription, c-terminal polypurine tract (PPT) for the initiation of the plus strand synthesis[16,17](Fig. 1). Although there can be recombinational deletion in these sequences with molecular evolution in different groups of ERVs[18]. One of the most convenient methods to differentiate

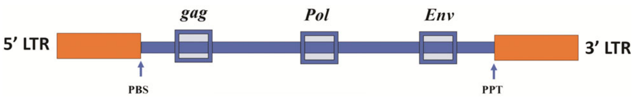

Fig. 1 — Schematic structure of an endogenous retrovirus with its usual components, such as 5′ long terminal repeat (5 LTR), primer binding site (PBS), *gag*(matrix capsid and nucleocapsid proteins), *pol* (polymerase), *env* (envelope), *PPT* (poly purine tract) and 3′ LTR.

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these viruses is based on the specific host tRNA used as a primer for reverse transcription, designated as tRNA^X, where X represents the one-letter amino acid code of the amino acid carried by that tRNA, for example, ERV-K′s primer tRNA is exclusive to lysine (K)[19]. The subsequent subsections explore the evolutionary trajectories and host genome interactions of specific ERVs, spanning from ancient lineages to recent insertions. These ERV families mark distinct integration periods in simian and human evolution and provide a basis for connecting phylogeny to immune regulation.

Endogenous Retrovirus-E

The ERV-E is one of the oldest viruses endogenised in the primates and categorized into two groups (Group I & Group II) based on *env* sequences insertion[20](Fig. 2). Group II is integrated into the OWM genome 40-50 million years ago (MYA). The group I integrated in hominoid′s (Apes and Humans) genomes approximately 5-20 MYA. Yi & Kim[20] also demonstrated that 3 different types of LTRs (LTR2, LTR2B and LTR2C). The LTRs are differentiated on the basis of their U3, R and U5 sequence regions and integrated into primates with their advancement[21]. While the segregation of NWM from the OWMs, ERV-E shifted its fate only towards the hominoidsand disappeared in the NWMs[22]. The ERV-E sequences become adapted to the host genome and contribute to genes such as *CD5* and *FABP7*, incorporating additional promoters and exons. This produces variants of CD5 and FABP7 proteins in specific clinical conditions, i.e. leukaemia[23,24]. However, this promoter shift is exclusive to humans and has not been well researched in other simians. Investigations in other simian species that are specific to these genes can provide a better understanding of ERV-E evolution and its relationship with the host genome.

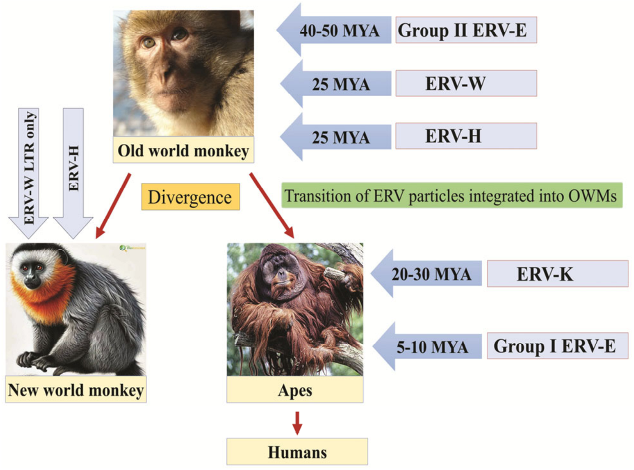

Fig. 2 —Integration periods (in Million Years Ago; MYA) of different types of endogenous retroviruses (ERVs) in the simians and humans. Also, their presence in the New World monkeys post-divergence. The old world monkey (Rhesus) figure is taken from the website “US represented” (https://usrepresented.com/2015/04/10/rhesus-macaques/). New world monkeys Alta Floresta TitiMonkey illustration from the website “BIOEXPLORER” (https://www.bioexplorer.net/animals/mammals/monkeys/alta-floresta-titi/). Ape figure is of a Flanged male Bornean orangutan (Pongo pygmaeus) © David Lawson / WWF-UK (https://wwf.panda.org/discover/knowledge_hub/endangered_species/great_apes/orangutans/).

Endogenous Retrovirus-K

The ERV-K is the most recent retrovirus endogenised in simians and humans and extensively researched as HERV[25,26]. Most of HERV-Ks, which are integrated into human genomes, are endogenised (20-30 MYA), while the divergence of humans from chimpanzee[27,28]. Based on phylogeny, the LTRs of the ERV-K are divided into three groups: LTR5A, LTR5B, and LTR5Hs[29]. After LTRs, when we look for the internal sequences of the virus, there are deletions in the viral regions like *gag* and *env* of HERV-K identified by Tonjes *et al.*[30] when compared to an almost intact virus in the chromosome 7 of the human genome[31]. The deletions in viral sequences are crucial for explaining their phylogenetic fate, whether or not they are relevant to their hosts. The variations in the HERV-K provirus sequences lead to the generation of different subtypes like HERV-K9, HERV-K10 and HERV-K70 based on the percentage of sequence homology with the original provirus (denoted by a number at the end of the nomenclature, e.g. 10% homology in case of HERV-K10)[32]. Interestingly, Holloway *et al.*[33] have shown that the endogenisation of the HERV-K in Gorillas occurs more recently than in Chimps and humans. This is the reflection of a broad phylogenetic divergence event of Gorillas from chimpanzees[34]. Similarly, the HERV-Ks can become an essential marker for the phylogenetic analysis of primates.

Endogenous Retrovirus-W

The HERV-W is known as the multiple-sclerosis-associated retrovirus (MSRV) because its particles were first isolated from the multiple sclerosis (MS) derived monocytes[35]. Its *pol* region is detected in the OWMs, apes, and humans, but not in the NWMs.

Moreover, the LTRs of HERV-W can be found in all simians and humans. This indicates the independent evolution of the viral particles throughout the evolution[36,37].

Endogenous Retrovirus-H

ERV-Hs are one of the most abundant exogenous particles assembled in the human genome and are categorised into three groups (I,II&III) based on *env* sequences. Group I is the major one found in humans and African great apes, and it includes HERV-H10, HERV-H19 and HERV-H/env62, etc.[38]. The LTR-based analysis by Goodchild *et al.*[39] shows that the ERV-H was integrated into simians before the divergence of the Apes from the OWMs. ERV-H elements were also found in the NWMs in very low numbers, which means the large no. of ERV-H elements were excluded post OWM-NWM segregation in the NWMs[40]. Apart from the evolutionary changes in the simians and humans, when we look for the activity of HERV-H, the env of HERV-H19 was first found to be involved in the expression of a protein equivalent to the immunosuppressive peptide CKS-17 and implicated in human health[41]. Importantly, the HERV-H particles are constitutively expressed in the embryonic stem cells (ESCs) and regarded as the pluripotency markers[42]. Gemmell *et al.*[43] further explained that the *gag* protein of the virus acts as a transcription factor in ESCs. The evolutionary changes in this abundant group of HERV have definite roles in shaping the genome of their hosts.

The evolutionary history of these viral lineages highlights how deeply they are embedded in the primate genome, and their current importance is best seen in their roles in human immune system diseases.

Implications of the HERVs in human immune disorders

HERVs make up about 8% of the human genome and are remnants of ancient retroviral infections integrated into germline DNA[44]. Most of these viral sequences are epigenetically silenced and cannot replicate, but growing evidence shows that some HERV elements can be transcriptionally reactivated during inflammation, infection, or epigenetic dysregulation[45]. When reactivated, HERVs may influence immune homeostasis by altering gene expression, producing viral proteins that trigger immune responses, and activating both innate and adaptive immunity[46]. Consequently, abnormal HERV activity is increasingly associated with immune system problems and disease development. Although the HERVs are broadly implicated in two categories of disorders: (a) Malignancies, (b) Autoimmune conditions.

Malignancies

The involvement of the ERVs in cancers is well established in humans. Also, they can entangle with the host immune system specifically[47]. Saini *et al.*[48] have uncovered several ERV-derived peptides in the case of myeloid malignancies targeted by the host T-cells. This indicates that the ERV particles are not only involved in the malignancies but also entangle with the immune system and can be targeted as immunotherapeutic targets. Similarly, HERV-K9 particles, which were seen overexpressed in acute myelocytic leukaemia (AML) patients, can be targeted for therapeutic purposes[49]. In continuation of the screening of ERVs in the case of blood cancers, the overexpression of the ERV RNAs in chronic lymphocytic leukaemia (CLL) patients was observed by Ferlita *et al.*[50]. Furthermore, when we look for the specific ERV gene involvement, it was investigated that the *np9* gene of HERV-K is overexpressed in the CLL patients[51]. Not the *np9* gene product alone, but the HERV-R*env*protein in combination was potentially involved in paediatric acute lymphoblastic leukaemia (PALL)[52].

The HERV-W envelope protein syncytin, which has a critical role in placental morphogenesis, was detected in a broad range of leukaemia and lymphoma patients[53]. The absence of syncytin in healthy blood donors suggests that it can be recognised as a marker of blood cancers[53]. As we mentioned earlier about the integration of the HERV-E sequence upstream to the *CD5* gene, where the integration influences the *CD5* gene and provides an additional exon which expressed exclusively in the case of B-cell CLL and T-cell acute lymphoblastic leukaemia (T-ALL)[24,54-56]. Research on the role of endogenous retroviruses (ERVs) in blood cancers is still in its early stages, and current findings primarily reveal associations between ERV expression and blood cancers; additional evidence is needed to establish conclusive results. Nonetheless, growing evidence indicates that ERVs significantly contribute to haematological malignancies and engage actively with the immune system.

Autoimmunity

Autoimmunity occurs when the immune system mistakenly identifies its own antigens as foreign[57].

Expression of ERV superantigens, such as the *env* gene product of HERV-K18, known to trigger immune responses in various autoimmune diseases, including rheumatoid arthritis[58-60]. This discussion will focus on specific autoimmune conditions, such as Type-1 diabetes mellitus (T1DM), multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), where ERVs are involved.

T1DM is a condition where the cell-mediated immunity destroys the beta cells in the pancreas of patients[61]. Tovo *et al.*[62] have assessed the higher expression of HERV-W and HERV-H in the peripheral leukocytes of patients with new-onset T1DM. This suggests retroviral implications in the onset of the disease. It was also observed that the *env* proteins of the HERV-W were localised in the pancreas of the T1DM patients[63,64.] This is the case of direct involvement of any ERV in the exacerbation of autoimmunity by inducing inflammation and toxicity towards the pancreatic beta cells. The ERVs can be targeted to reduce the severity of T1DM, in which they are among the dominant factors that worsen the condition.

The neurodegenerative condition MS affects the central nervous system (CNS), where the myelin sheath of the nerves is damaged due to immunological reactions[65]. The HERV-W was previously known as the multiple sclerosis associated retrovirus (MSRV) due to its association with MS patients, where its envelope protein was detected in higher amounts in the serum[66]. The presence of HERV-W open reading frames (ORFs) at chromosome Xq22.3 makes the MS condition worse in women, when compared to men[67]. To limit the disease, natalizumab and temelimab antibodies have been shown to reduce the ERV-W's envelope protein expression[68,69]. However, more strategies are needed to significantly alleviate MS.

RA is a condition where the immune system attacks the own cell lining of joints and causes inflammatory arthritis[70.] Along with the genetic and environmental factors, the ERVs can also play a crucial role in the progression of RA. The ERV-K10 *gag* transcript was found to be overexpressed in RA patients when compared to healthy and osteoarthritis patients[71,72].Recently, the autoantibodies against the citrullinated envelope protein of the HERV-K have been detected in RA patients[73]. More research is going on to establish the strong relationship between RA and ERVs.

SLE is an inflammatory condition that affects multiple organ systems when the immune system becomes hyperactive[74]. The HTLV-1 Related Endogenous Sequence (HRES-1) produces a nuclear protein, which serves as the autoantigen in SLE patients, and is of endogenous retrovirus origin[75]. Tokuyama *et al.*[76] have unearthed that the autoantibodies developed against the HERV-K102 envelope protein promote the neutrophil phagocytosis and increase of the SLE severity. Interestingly, ERVs are not always the causative factors of SLE. Laska *et al.*[77] has shown that the immune system exploits the *Env59* gene of HERV-H to control its mess of SLE, when overexpression of the Env59 protein reduces the pro-inflammatory cytokine IL-6. The ERVs also have an indirect role in the induction of the innate immunity in SLE patients (Fig. 3).

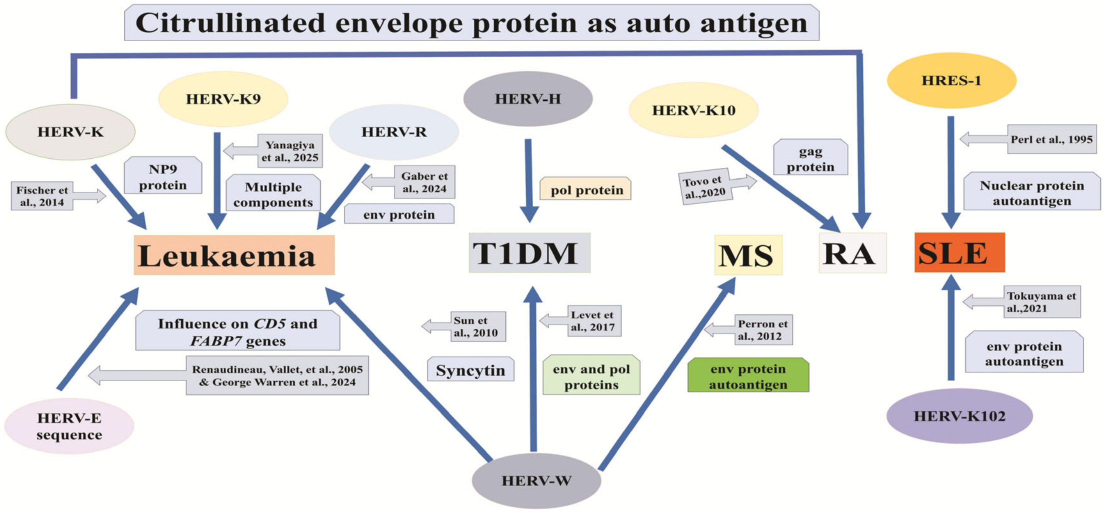

Fig. 3 —Implications of the different types of human endogenous retroviruses (HERVs) induced diseases concerning the immune system, including leukaemia, Type-1 diabetes mellitus (T1DM), Multiple sclerosis (MS), Rheumatic arthritis (RA) and Systemic lupus erythematosus (SLE).

Evolution and immunology

The information contained within sections 2 and 3 demonstrates that Endogenous Retroviruses (ERVs) are not merely ancient, inactive DNA segments; they also provide insights into the evolutionary history of primates and are directly or indirectly implicated in the primate immune system. In this discussion, the primary focus has been on the human immune system. Nonetheless, the dual roles of ERVs in primates have traditionally been examined separately. In this context, we have elucidated the evolution of HERVs in relation to the immune system.

ERV particles are traditionally considered one of the markers for analysing the evolutionary journey of primates[78,79]. Along with this evolutionary footprint, they also shape the immune systems of simians and humans. For example, MC132 is the immunosuppressive protein of ERV origin that is found throughout the monkeys, apes and humans[80]. Evolutionary and immunoregulatory roles of ERVs, coincide in primates for fitness and survival. However, these coincidences are not well-studied. One example of this perspective is the evolution of the *CD5* gene in association with the HERV-E endogenous retrovirus sequence[3]. CD5 is a cell surface protein expressed throughout the T-cells and in a limited population of the B-cells and has immunomodulatory roles[81]. The HERV sequence associated with *CD5* is inserted into primates after the OWM-NWM divergence and is present in all OWMs and apes[82]. But the HERV's masking effects on the *CD5* are detected only in humans. In humans, under disease conditions such as leukaemia, the HERV sequence causes alternative splicing of the *CD5* gene, adding 11 exons and replacing its first exon E1A with E1B[3,24]. Ultimately, it produces a variant of the CD5 protein that remains in the cytoplasm, unlike its classic surface form[54,83]. This exonal switching is influenced by polyaromatic hydrocarbons such as benzo[a]pyrene (BAP)[84]. However, the functional impact of this CD5 variant is still elusive. The fatty acid binding protein 7 (FABP7) is a cytoplasmic protein involved in growth and metabolism, and is overexpressed in various types of cancers[85]. In case of diffuse large B-cell lymphoma(DLBCL), Lock *et al.*[23] have detected overexpression of a FABP7 variant. Further analysis reveals that this variant arose due to a transposable element of ERV-E origin acting as a promoter. Direct interaction of ERVs with immunologically important genes influences primate species' evolutionary fitness[86]. However, ERV insertions are reliable phylogenetic markers. Still, most of the information about how ERVs affect the immune system comes from studies in humans, with only a few in non-human primates confirming these findings. Therefore, caution is advised when making broad evolutionary claims about ERV-related immune effects.

Additionally, this can impact their progress in a specific geographical area, such as humans originating on the African continent, spreading across the continents, and finding a suitable environment to flourish[87,88]. But the apes and OWMs have the variable genetic lineage in Asia and Africa, e.g. the African great apes, Chimpanzee and Gorilla, are evolutionary different from Asian apes, Orangutan and Gibbons, which may have a possible immune-evolutionary aspect[89-93] (Fig. 4).

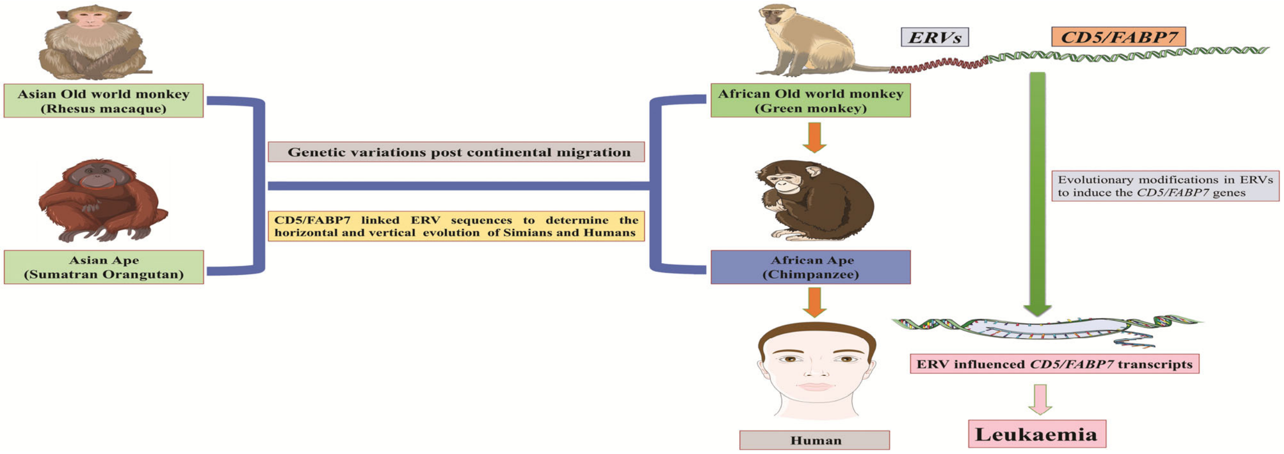

Fig. 4 —Endogenous retrovirus (ERV) linked evolution of the *CD5* and *FABP7*. The visible impact of ERVs on both genes can only be seen in humans. Also, these ERVs can act as determinants of phylogeny. Most of the Figure was made by utilising the pictures provided by Servier Medical Art (Servier; https://smart.servier.com/), licensed under a Creative Commons Attribution 4.0 Unported License. The Asian ape Sumatran orangutan image was downloaded from the Freepik website (https://www.freepik.com/vectors/sumatran-orangutan-side-view) operated by Freepik Company, S.L., registered in the Commercial Registry of Málaga.

However, the suggested correlations between geographical distribution (e.g., Africa and Asia) and ERV-associated immune evolution remain hypothetical and require additional comparative genomic and functional validation.

Conclusion

After considering all the points discussed earlier, it is clear that endogenous retroviruses have a significant impact on our immune system. This interaction can occur directly through viral particles or indirectly by altering the expression of genes involved in the immune system. Ultimately, the way ERV sequences regulate immunomodulatory genes influences the evolutionary fitness of humans and simians. This evolutionary fitness is exclusive to the genes associated with the ERV, which exhibit variable expression across simians and affect their health. By examining the relationship between ERV sequences and immunomodulatory genes, we can establish a phylogenetic connection between humans and simians. When used to determine primate phylogeny, ERV sequences may yield a distorted phylogram if linked to a gene crucial for immunity and health. This can also shed light on how simians evolved and spread across the continents.

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Conflict of interest

The authors declare no conflict of interest.

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